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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/402,394	03/10/1995	MICHAEL DORSCHUG	02481.0790-0	2561

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EXAMINER
SAOUD, CHRISTINE J

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/402,394	Applicant(s) DORSCHUG et al.
	Examiner Christine Saoud	Art Unit 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *21-23, 26, 27, 31, and 33-42* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *21-23, 26, 27, 31, and 33-42* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. In light of the comments of the Board in the Decision mailed 29 October 2002, prosecution in the instant application is REOPENED.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

3. Claim 33 is rejected under 35 U.S.C. 102(e) as being anticipated by Markussen et al. (U.S. Pat. 4,916,212).

Markussen et al. states that preferred insulin precursors includes those where m=1, n is most preferably 1-3 or 1-2 and that X is preferably Ala, Ser and Thr, X being equal or different. Thus, Markussen et al. is desribing a very limited subgenus of compounds as indicated in the Board decision (Appeal No. 2001-1586; see table at page 10 of the decision). The preferred embodiments in connection with the generic formula constitutes a description of a definite and limited class of compounds, and therefore, the compound of claim 33 is anticpated by Markussen. See In re Petering, 301 F.2d 676, 133 USPQ 275 (CCPA 1962).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claim 21 and 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Markussen et al. in view of Goeddel et al. (EPO 055,945), Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332).

Markussen et al. ('212) is as described above. This protein is a single peptide chain. This precursor is converted to human insulin by derivatization and treatment with trypsin. (See '212 at

column 2, line 65, through column 3, line 46; Examples 11, 13, and 16; and claims.) Fusion proteins and their cleavage from the precursor are disclosed. (See column 5, lines 11-20.) DNA sequence encoding the insulin precursor, expression vectors, transformed cells, and recombinant methods of production in yeast (as well as *E. coli* holding plasmids encoding the desired insulin precursors) are also disclosed and claimed. Markussen et al. does not specifically teach the preparation of mono-Arg-insulin which includes the use of trypsin as cleavage agent for generation of mono-Arg-insulin.

The miniproinsulin of the instant application is directed to a single peptide chain of the formula B(1-30)-Arg-A(1-21). The amino acid at position 30 in native human insulin is Thr. This position is equivalent to the "X" of Markussen et al.

Goeddel et al. teach producing recombinant fusion proteins of insulin precursors to another protein and cleaving them. The reference further teaches making a fusion protein with an insulin variant in which the C chain of insulin contains only six amino acids. (See page 6, line 19 through page 8, line 2; abstract; claims; pages 26-27.) Goeddel et al. also teaches production in E. coli. With regard to fusion proteins, it is noted that *E. coli* has long been used to produce desirable precursors to insulin and that fusion proteins are often used for small peptides.

Grau ('684) teaches using trypsin and carboxypeptidase B simultaneously to produce mature insulin from proinsulin. (See column 5, lines 49-59.)

Grau ('332) teaches that treatment of proinsulin with trypsin alone gives intermediates with an arginine at B31. This insulin-Arg^{B31}-OH derivative is stable to further tryptic degradation.

Enzymes having both tryptic and carboxypeptidase B activity are required to produce insulin. (See column 1, lines 1-32; column 2, lines 10-12.) The intermediate disclosed by Grau ('332) is the mono-Arg-insulin of formula II in the instant claims.

Markussen et al. teaches the claimed miniproinsulin precursor (102 rejection above for claim 33), DNA sequences encoding it, vectors, host cells and process for preparation where "X" is Thr, "n" is 1, and "Y" is Arg. The prior art teaches Applicant's claimed composition in method step (a). It would have been obvious to make fusion proteins as taught by Goeddel et al. using the insulin precursor, DNA sequences, and vectors taught by Markussen et al. for the production of the mono-Arg-insulin of Markussen et al. and to cleave the fusion protein to release the desired protein as taught by Goeddel et al. One would have been motivated by the known benefits of producing small peptides as fusion proteins in bacterial and yeast hosts and the success with another insulin variant in which the C chain is shortened and because the usefulness of fusion proteins is suggested by Markussen et al. It would have been obvious to prepare mono-Arg-insulin by expressing a DNA molecule encoding miniproinsulin in bacteria as taught and suggested by Markussen et al. and cleaving this compound with trypsin as taught by Grau ('332 and '684) to produce mono-Arg-insulin. One would have been motivated to produce this stable intermediate of insulin for further treatment with carboxypeptidase B to produce insulin for treating diabetes. The limitation of "under conditions where no crystals are formed" is met in that the methods of Markussen demonstrate that the processes take place in an aqueous buffer (acetic acid) with the isolation of the protein via precipitation with acetone (see column 18, lines 42-68 of

Markussen '212). Finally, it would have been obvious to one of ordinary skill in the art at the time the invention was made to precipitate the resulting mono-Arg-insulin for the isolation of the desired product as taught by Markussen '212 (column 18, lines 42-68). Therefore, the invention as a whole would have been *prima facie* obvious at the time it was made, absent clear and convincing evidence to the contrary.

6. Claim 25 and 37-38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212) in view of Goeddel et al. (EPO 055,945), Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332) further in view of Mai et al. as applied above.

The disclosures of Markussen et al., Goeddel et al. and Grau are as described above. These references do not specifically teach the bridging member Met-Ile-Glu-Gly-Arg of step (a) in the claim.

Mai et al. teach that it would have been well known in the art to use common cleavage sites in fusion proteins. The reference teaches that cyanogen bromide cleaves after the amino acid Met and that factor Xa cleaves after the tetrapeptide Ile-Glu-Gly-Arg. (See column 3, line 14, through column 4, line 35, especially column 3, line 67, through column 4, line 1; and column 9, lines 7-19.)

It would have been obvious to make the miniproinsulin of Markussen et al. as a fusion protein using the cleavable sequence Met-Ile-Glu-Gly-Arg as taught in Mai et al. for the production of mono-Arg-insulin of Grau. Markussen et al. suggest making fusion proteins that

can be cleaved as does Goeddel et al. The recited sequence of the claim includes cleavage sites for cyanogen bromide and factor Xa that would have been commonly used in fusion proteins and would have been well known to the skilled artisan. One would have been motivated to make a fusion protein for the reasons taught by Markussen et al., Goeddel et al., and Mai et al. and to use this construct in the method of making mono-Arg-insulin of Grau for the advantages taught therein, absent clear and convincing evidence to the contrary. Therefore, the invention as a whole would have been *prima facie* obvious at the time it was made, absent clear and convincing evidence to the contrary.

7. Claims 22, 23, 40-41 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212)in view of Goeddel et al. (EPO 055,945), Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332).

The disclosures of Markussen et al., Goeddel et al. and Grau are as described above. Markussen et al. do not teach a method of making insulin using both trypsin and carboxypeptidase B to convert miniproinsulin to mono-Arg-insulin and then to insulin.

It would have been obvious to use both trypsin and carboxypeptidase B to convert the miniproinsulin of Markussen et al. (having the formula B(1-30)-Arg-A(1-21)) first to mono-Arg-insulin and then to insulin. Grau ('332) teaches that mono-Arg-insulin can be formed by trypsin cleavage and that this form is resistant to further tryptic degradation and Grau ('684) teaches that the combination of trypsin and carboxypeptidase B together can convert proinsulin to insulin. One would have been motivated to use both trypsin and carboxypeptidase B in order to produce

insulin from the precursor of Markussen et al. for treating diabetes. The limitation of "under conditions where no crystals are formed" is met in that the methods of Markussen demonstrate that the processes take place in an aqueous buffer (acetic acid) with the isolation of the protein via precipitation with acetone (see column 18, lines 42-68 of Markussen '212). It also would have been obvious to one of ordinary skill in the art at the time the invention was made to precipitate the resulting mono-Arg-insulin for the isolation of the desired product as taught by Markussen '212 (column 18, lines 42-68). Finally, claim 23 requires that the trypsin and carboxypeptidase B be added in the same vessel; Grau '684 teaches the process wherein trypsin and carboxypeptidase B were added together (i.e. in the same vessel) and resulted in the production of mature insulin from proinsulin (see column 5, lines 57-59). Therefore, the invention as a whole would have been *prima facie* obvious at the time it was made, absent clear and convincing evidence to the contrary.

8. Claims 26-27 and 31-32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212) in view of Goeddel et al. (EPO 055,945), Mai et al., Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332).

The disclosures of Markussen et al., Goeddel et al., Grau and Mai et al. are as described above. None of these references teach the method of the claims in its entirety. Claims 26-27 and 31-32 are directed to methods using both trypsin and carboxypeptidase B to convert miniproinsulin to mono-Arg-insulin and then to insulin, including a bridging member Met-Ile-Glu-Gly-Arg between the fusion protein and the miniproinsulin. Claims 31-32 also include the limitation of "without formation of substantial amounts of insulin Des-B30".

It would have been obvious to use both trypsin and carboxypeptidase B to convert the miniproinsulin of Markussen et al. (having the formula B(1-30)-Arg-A(1-21)) first to mono-Arg-insulin and then to insulin. Grau ('332) teaches that mono-Arg-insulin can be formed by trypsin cleavage and that this form is resistant to further tryptic degradation and Grau ('684) teaches that the combination of trypsin and carboxypeptidase B together can convert proinsulin to insulin. One would have been motivated to use both trypsin and carboxypeptidase B in order to produce insulin from the precursor of Markussen et al. for treating diabetes. It would have been obvious to make the miniproinsulin of Markussen et al. as a fusion protein using the cleavable sequence Met-Ile-Glu-Gly-Arg as taught in Mai et al. for the production of mono-Arg-insulin of Grau. Markussen et al. suggest making fusion proteins that can be cleaved as does Goeddel et al. The recited sequence of the claim includes cleavage sites for cyanogen bromide and factor Xa that would have been commonly used in fusion proteins and would have been well known to the skilled artisan. One would have been motivated to make a fusion protein for the reasons taught by Markussen et al., Goeddel et al., and Mai et al. and to use this construct in the method of making mono-Arg-insulin of Grau for the advantages taught therein, absent clear and convincing evidence to the contrary. The limitation of "under conditions where no crystals are formed" is met in that the methods of Markussen demonstrate that the processes take place in an aqueous buffer (acetic acid) with the isolation of the protein via precipitation with acetone (see column 18, lines 42-68 of Markussen '212). It also would have been obvious to one of ordinary skill in the art at the time the invention was made to precipitate the resulting mono-Arg-insulin for the

isolation of the desired product as taught by Markussen '212 (column 18, lines 42-68). Claim 27 requires that the trypsin and carboxypeptidase B be added in the same vessel; Grau '684 teaches the process wherein trypsin and carboxypeptidase B were added together (i.e. in the same vessel) and resulted in the production of mature insulin from proinsulin (see column 5, lines 57-59). Lastly, claims 31 and 32 recite "without formation of substantial amounts of insulin Des-B30. One of ordinary skill in the art would not expect the methods of Markussen et al. and Grau for the production of insulin from miniproinsulin and mono-Arg-insulin to result in the formation of substantial amounts of Des-B30 insulin, nor are there any steps in the instant claims which would distinguish from the prior art in resulting in different amounts of Des-B30 insulin, absent clear and convincing evidence to the contrary. Therefore, the invention as a whole would have been *prima facie* obvious at the time it was made, absent clear and convincing evidence to the contrary.

9. Claims 39 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Markussen et al. in view of Grau ('684) and Grau ('332).

The references are as described above. It would have been prima facie obvious to one of ordinary skill in the art to prepare the mono-Arg-insulin by expressing a DNA molecule encoding miniproinsulin in either bacteria or yeast as taught by Markussen et al. and cleaving this compound with trypsin as taught by Grau ('332 and '684) to produce the mono-Arg-insulin of Markussen et al.. One would have been motivated to produce a stable intermediate of insulin for further treatment with carboxypeptidase B to produce insulin for treating diabetes and because this molecule is specifically taught in Markussen et al.. One would further be motivated to make

the mono-Arg-insulin of Markussen et al. because Grau ('332) teaches that mono-Arg-insulin is resistant to further tryptic degradation, and would therefore, be a stable intermediate for the future formation of insulin.

Conclusion

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Christine J. Saoud, Ph.D., whose telephone number is (703) 305-7519. The Examiner can normally be reached on Monday to Thursday from 8AM to 2PM. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. §§ 1.6(d) and 1.8). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternate number. Official papers filed After Final rejection filed by fax should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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